Tetrahedron Letters 55 (2014) 1621–1624

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Formal synthesis of (±)-cladoniamide G

Paiboon Ngernmeesri *, Sarochar Soonkit, Anothai Konkhum, Boonsong Kongkathip

Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Kasetsart University, Bangkok 10900, Thailand

ARTICLE INFO

Article history:
Received 27 November 2013
Revised 10 January 2014
Accepted 21 January 2014
Available online 28 January 2014

Keywords:
Natural product synthesis
Anticancer
(±)-Cladoniamide G
Suzuki–Miyaura coupling

ABSTRACT

The formal synthesis of (±)-cladoniamide G, a natural product that exhibits cytotoxicity against human breast cancer MCF-7 cells, is presented. Our strategy employed a Suzuki–Miyaura coupling to join the two indole subunits of this natural product.

Indolocarbazole alkaloids such as staurosporine (**1**) and rebeccamycin (**2**) (Fig. 1) have drawn considerable attention from the synthetic community because of their numerous interesting biological activities, especially in the area of oncology.[1–3] In 2008, the Anderson group reported the isolation and structure determination of cladoniamides A-G from cultures of *Streptomyces uncialis* obtained from the lichen, *Cladonia uncialis*.[4] These natural products represent a new class of alkaloids that possess an unprecedented indolotryptoline skeleton, which has one of its indole subunits flipped within the indolocarbazole. Investigations on these alkaloids have revealed that only cladoniamides A (**3**) and G (**4**) possess significant biological activities, having cytotoxicity against human colon cancer HCT116 cells (8.8 ng/mL)[5] and human breast cancer MCF-7 cells (10 μg/mL),[4] respectively. The absolute stereochemistry of cladoniamide A has been assigned as shown in Figure 1 by single crystal X-ray diffraction. Since cladoniamides A and G are likely to be biosynthetically related, the absolute configuration of cladoniamide G can be inferred.[4]

Our aim was to develop a strategy to synthesize cladoniamide G and a set of its structural analogs with various substituents on both indole moieties. Scheme 1 depicts our retrosynthetic analysis of cladoniamide G. We envisioned that this alkaloid could be derived from dioxo-bisindole **5**, which could in turn be prepared from bisindole **6**. The two indole fragments of **6** could be joined together by a Suzuki–Miyaura coupling reaction of bromoindole **7** and boronic acid **8**, which could both be prepared in a few steps from commercially available indole derivatives. Although Pd-catalyzed cross-coupling reactions have gained popularity and are widely

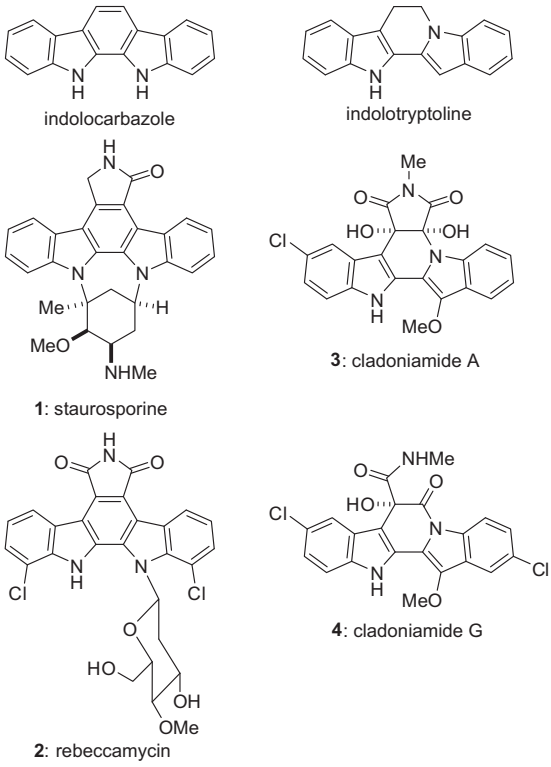
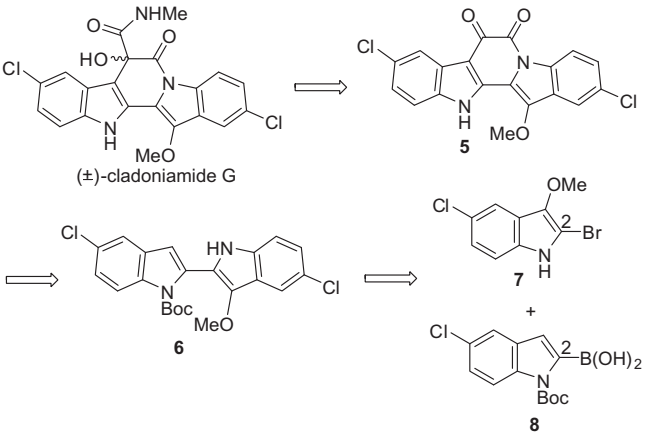


Figure 1. Cladoniamides A and G and related bisindole alkaloids.

* Corresponding author. Tel.: +66 2 562 5555x2202; fax: +66 2 579 3955.
E-mail address: fscipbn@ku.ac.th (P. Ngernmeesri).

http://dx.doi.org/10.1016/j.tetlet.2014.01.086
0040-4039/

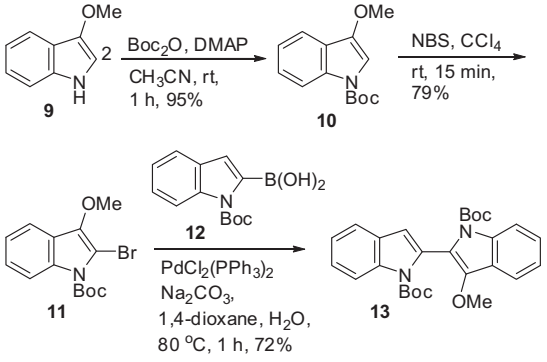


Scheme 1. Retrosynthetic analysis of (±)-cladoniamide G.

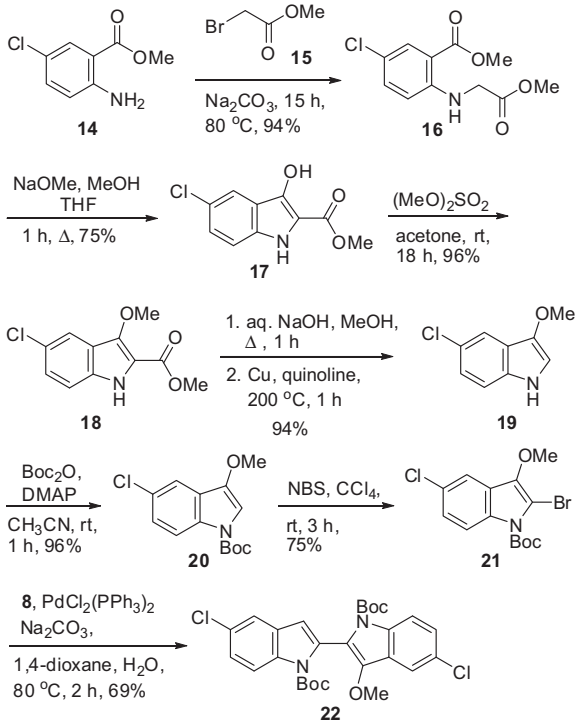
used in natural product synthesis, only a few examples of C2–C2′ indole–indole couplings have been reported.[6] Therefore, we were interested in further exploring this area, and expanding upon it, by coupling indoles with novel substitution patterns. This coupling strategy would allow us to easily prepare a number of different analogs by varying the substituents on the starting materials **7** and **8**.

To test the feasibility of our cross-coupling strategy, we began a model study with 3-methoxyindole (**9**)[7] as shown in Scheme 2. Attempts to brominate **9** at C2 with NBS at 0 °C resulted in none of the desired product, and when the temperature was raised to room temperature, decomposition occurred. Surprisingly, bromination of the more electron-deficient *N*-Boc-3-methoxyindole (**10**) took place easily to give bromoindole **11**. TLC analysis showed that the starting material was completely consumed within 15 minutes, and the desired bromoindole was produced exclusively. However, this compound was quite unstable and decomposed rapidly when the crude product was either purified on silica gel or carried on to next step. Fortunately, purification by flash chromatography on basic alumina gave compound **11** in a decent yield (79%). To our delight, the Suzuki–Miyaura coupling reaction of **11** with indolyl boronic acid **12**[8] in the presence of catalytic $PdCl_2(PPh_3)_2$ generated bisindole **13** in 72% yield.[9]

With this promising result, we synthesized the 5-chloro analog of **11** as outlined in Scheme 3. Methoxy indole ester **18** was prepared according to the methods described by Dropinski[10] and Bös[11] with minor modifications. In the second step, NaOMe/MeOH was used instead of NaOEt/EtOH to generate methyl carboxylate **17**. TLC analysis showed almost exclusively carboxylate **17**, but only a 75% yield was obtained due to isolation problems.

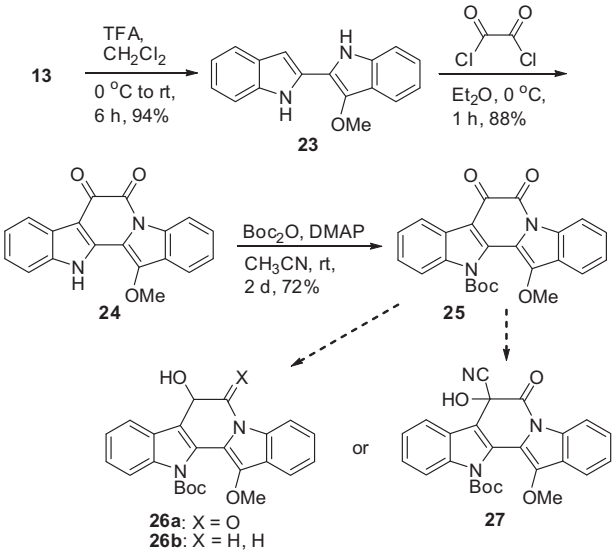


Scheme 2. Model study on the Suzuki coupling reaction.



Scheme 3. Synthesis of bisindole **22**.

Nevertheless, this yield was comparable to that reported by Bös (79% yield for the ethyl analog of **17**). It should be noted that our attempts to use NaOEt/EtOH produced both **17** and its ethyl analog in an approximate 1:1 ratio. In addition, dimethyl sulfate was used in place of diazomethane to generate methoxy indole **18**, due to safety concerns, and did not compromise the yield. The ester group of compound **18** was then hydrolyzed by aq NaOH and the resulting carboxylic acid was decarboxylated using copper powder in quinoline according to the method described by Cook[12] to give 5-chloro-3-methoxyindole (**19**) in excellent yield. Similar to **9**, bromination of **19** resulted in decomposition, but bromination of the *N*-Boc indole **20** went on smoothly to generate bromoindole **21** in 75% yield. Compared to the bromination of **10**, this reaction took

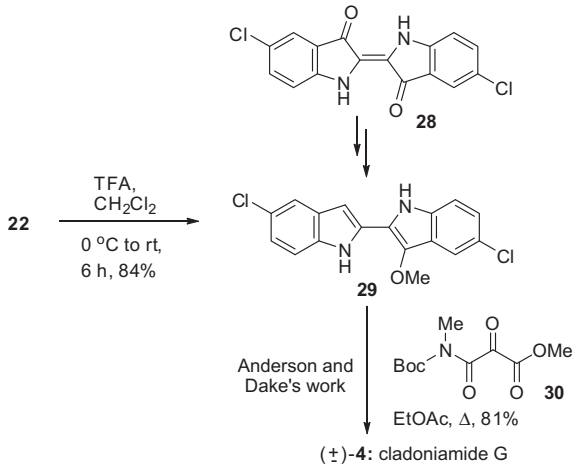


Scheme 4. Synthesis of dioxo-bisindole **25**.

much longer to go to completion (3 h vs 15 min), presumably due to the decreased nucleophilicity of the substrate brought about by the electron-withdrawing Cl substituent. However, both reactions gave the desired products in comparable yields. Finally, the Suzuki–Miyaura coupling of **21** and boronic acid **8**[8] provided the desired bisindole **22** in reasonable yield (69%).

As a final test of our strategy, we employed bisindole **13** (Scheme 4). Removal of the Boc groups of **13** with TFA provided *N*,*N*′-unprotected bisindole **23** in 94% yield. When **23** was treated with oxalyl chloride in diethyl ether at 0 °C, dioxo-bisindole **24** formed immediately and then precipitated as a red solid. This solid was easily collected by removal of the solvent and rinsing with ether/hexanes. ^{1}H NMR spectroscopy of the red solid showed exclusively the desired product so no further purification was required. Attempts to modify the carbonyl group of **24** were problematic as this compound was not soluble in most organic solvents. Therefore, the indole NH of **24** was reprotected with a Boc group to make it less polar. In addition, this protecting group would serve as an electron-withdrawing group to increase the electrophilicity of the keto carbonyl. It should be noted that this protection reaction took two days instead of a few minutes, presumably due to the insolubility of **24** in CH_3CN as well as the steric hindrance imparted by the methoxy group. Although the problem with solubility was solved, our attempts to reduce or add a nucleophile to the keto carbonyl group to form compounds **26a** or **27** were unsuccessful. For example, both of the carbonyl groups of **25** were easily reduced with $NaBH_4$ to form **26b** as indicated by LRMS (m/z = 405.1) and ^{1}H NMR (1H at 4.12 ppm, dd, J = 8.5, 11.0 Hz and 1H at 3.74 ppm, dd, J = 4.9, 10.9 Hz) data of the isolated, but impure product. Unfortunately, this product decomposed within hours after isolation, so no further purification was performed. Moreover, an alternative route with the addition of CN^- to the carbonyl in DMSO also resulted in decomposition.

During our investigations to complete the synthesis of cladoniamide G, Anderson and Dake reported the total synthesis of this natural product from 5-chloroindole in five steps with 15% overall yield.[13] Their strategy was to prepare 5,5′-dichloroindigo (**28**) and transform it into bisindole **29** (Scheme 5). This compound was then converted into (±)-cladoniamide G in 81% yield when treated with linchpin reagent **30**, which was prepared from dimethyl malonate and benzaldehyde in four steps. Intermediate **29** could also be produced from our synthetic route in 84% yield when di-Boc bisindole **22** was treated with TFA. Hence, we report here the formal synthesis of (±)-cladoniamide G.



Scheme 5. Formal synthesis of (±)-cladoniamide G.

In summary, we were able to synthesize bisindole **29** in nine steps with 27% overall yield from methyl 2-amino-5-chlorobenzoate (**14**). The reaction of this bisindole precursor **29** and linchpin reagent **30** was reported earlier by Anderson and Dake to produce (±)-cladoniamide G. Although our route to prepare **29** is longer, good-to-excellent yields were obtained in each step in the synthesis resulting in a higher overall yield. In addition, our strategy to couple two indole subunits together would allow us to vary the substituents on each indole unit independently, and this modification could not be achieved with the route reported by Anderson and Dake.

Acknowledgments

Financial support was provided by the Thailand Research Fund (MRG5380301), the Center of Excellence for Innovation in Chemistry (PERCH-CIC), the Office of the Higher Education Commission, the Ministry of Education, the Faculty of Science, Kasetsart University, and Kasetsart University Research and Development Institute (KURDI). The authors thank the Chulabhorn Research Institute for providing high-resolution mass spectra.

Supplementary data

Supplementary data (Experimental procedures and characterization data for **10**–**11**, **13**, **16**–**25** and **29**.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.086.

References and notes

1. For a review on the synthesis of indolocarbazole alkaloids, see: Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303–4427.
2. For the synthesis of staurosporine and related compounds, see: (a) Link, J. T.; Gallant, M.; Danishefsky, S. J.; Huber, S. *J. Am. Chem. Soc.* **1993**, *115*, 3782–3783; (b) Link, J. T.; Raghavan, S.; Danishefsky, S. J. *J. Am. Soc. Chem.* **1995**, *117*, 552–553; (c) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825–2842; (d) Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Soc. Chem.* **1996**, *118*, 10656–10657; (e) Stoltz, B. M.; Goodman, S. N.; Onwueme, K. *J. Am. Chem. Soc.* **1997**, *119*, 9652–9661; (f) Moody, C. J.; Rahimtoola, K. F.; Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105–2114; (g) Mahboobi, S.; Eibler, E.; Koller, M.; Kumar, K. C. S.; Popp, A. *J. Org. Chem.* **1999**, *64*, 4697–4704; (h) Chen, S.-Y.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *J. Org. Chem.* **2001**, *66*, 5627–5628; (i) Rajeshwaran, G. G.; Mohanakrishnan, A. K. *Org. Lett.* **2011**, *13*, 1418–1421.
3. For the synthesis of rebeccamycin and related compounds, see: (a) Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 4015–4018; (b) Gallant, M.; Link, J. Y.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 343–349; (c) Faul, M. M.; Winneroske, L. L.; Krumrich, C. A. *J. Org. Chem.* **1999**, *64*, 2465–2470; (d) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841–7844; (e) Moreau, P.; Anizon, F.; Sancelme, M.; Prudhomme, M.; Severe, D.; Riou, J.-F.; Goossens, J.-F.; Hénichart, J.-P.; Bailly, C.; Labourier, E.; Tazzi, J.; Fabbro, D.; Meyer, T.; Aubertin, A. M. *J. Med. Chem.* **1999**, *42*, 1816–1822.
4. Williams, D. E.; Davies, J.; Patrick, B. O.; Bottriell, H.; Tarling, T.; Roberge, M.; Anderson, R. *Org. Lett.* **2008**, *10*, 3501–3504.
5. Chang, F. Y.; Brady, S. F. *J. Am. Chem. Soc.* **2011**, *133*, 9996–9999.
6. (a) Merlic, C. A.; McInnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 7661–7664; (b) Merlic, C. A.; You, Y.; McInnes, D. M.; Zechman, A. L.; Miller, M. M.; Deng, Q. *Tetrahedron* **2001**, *57*, 5199–5212; (c) Yamabuki, A.; Fujinawa, H.; Choshi, T.; Tohyama, S.; Matsumoto, K.; Ohmura, K.; Nobuhiro, J.; Hibino, S. *Tetrahedron Lett.* **2006**, *47*, 5859–5861; (d) Tohyama, S.; Choshi, T.; Matsumoto, K.; Yamabuki, A.; Hieda, Y.; Nobuhiro, J.; Hibino, S. *Heterocycles* **2010**, *82*, 397–416; (e) Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768–10771; (f) Matsumoto, K.; Choshi, T.; Hourai, M.; Tohyama, S.; Nobuhiro, J.; Hibino, S.; Zamami, Y.; Sasaki, K.; Abe, T.; Ishikura, M.; Hatae, N.; Iwamura, T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4762–4764; (g) Palmisano, G.; Santagostino, M. *Helv. Chim. Acta* **1993**, *76*, 2356–2366; (h) La Regina, G.; Bai, R.; Rensen, W. M.; Di Cesare, E.; Coluccia, A.; Piscitelli, F.; Famiglini, V.; Reggio, A.; Nalli, M.; Pelliccia, S.; Da Pozzo, E.; Costa, B.; Granata, I.; Porta, A.; Maresca, B.; Soriani, A.; Iannitto, M. L.; Santoni, A.; Li, J.; Cona, M. M.; Chen, F.; Ni, Y.; Brancale, A.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Martini, C.; Hamel, E.; Lavia, P.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2013**, *56*, 123–149.
7. Although 3-methoxyindole is commercially available, this compound was synthesized in our laboratory according to the procedure outlined in Scheme 3.
8. Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551–7552.

9. Our model study was reported at the Pure and Applied Chemistry International Conference in January 2013 (Ubon Ratchathani, Thailand).
10. Dropinski, J. F.; Akiyama, T.; Einstein, M.; Habulihaz, B.; Doebber, T.; Berger, J. P.; Meinke, P. T.; Shi, G. Q. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5035–5038.
11. Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J. L.; Mutel, V.; Sleight, A. J.; Widmer, U. *Eur. J. Med. Chem.* **1997**, *32*, 253–261.
12. Lui, R.; Zhang, P.; Gan, T.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 7447–7456.
13. Looseley, B. C.; Anderson, R. J.; Dake, G. R. *Org. Lett.* **2013**, *15*, 1152–1154.